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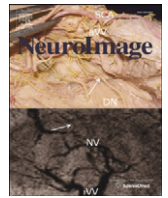
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Intrinsic variability in the human response to pain is assembled from multiple, dynamic brain processes

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ABSTRACT

The stimulus-evoked response is the principle measure used to elucidate the timing and spatial location of human brain activity. Brain and behavioural responses to pain are influenced by multiple intrinsic and extrinsic factors and display considerable, natural trial-by-trial variability. However, because the neuronal sources of this variability are poorly understood the functional information it contains is under-exploited for understanding the relationship between brain function and behaviour. We recorded simultaneous EEG–fMRI during rest and noxious thermal stimulation to characterise the relationship between natural fluctuations in behavioural pain-ratings, the spatiotemporal dynamics of brain network responses and intrinsic connectivity. We demonstrate that fMRI response variability in the pain network is: dependent upon its resting-state functional connectivity; modulated by behaviour; and correlated with EEG evoked-potential amplitude. The pre-stimulus default-mode network (DMN) fMRI signal predicts the subsequent magnitude of pain ratings, evoked-potentials and pain network BOLD responses. Additionally, the power of the ongoing EEG alpha oscillation, an index of cortical excitability, modulates the DMN fMRI response to pain. The complex interaction between alpha-power, DMN activity and both the behavioural report of pain and the brain's response to pain demonstrates the neurobiological significance of trial-by-trial variability. Furthermore, we show that multiple, interconnected factors contribute to both the brain's response to stimulation and the psychophysiological emergence of the subjective experience of pain.

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Introduction

In the course of everyday life the human brain is continually bombarded by sensory information and generates a behavioural response proportionate to the varying intensity and saliency of each event. Functional neuroimaging experiments simulate a constrained version of this scenario in a laboratory environment and primarily use the signal change evoked in response to a stimulus event to elucidate the timing, intensity and spatial location of the underlying brain activity. Conventional fMRI and EEG analyses assume that the brain's response is standardised and consistent across repeated stimulus presentations. However, studies ranging from single-neuron recordings to macroscale neuroimaging indicate that not only is response variability intrinsic to brain function but that it contains perceptually relevant information (Debener et al., 2006; Scaglione et al., 2011; Scheibe et al.,

2010). The functional and behavioural significance of this variability and the neural substrates underlying it remain poorly understood.

Human pain is a conscious, subjective interpretation of nociceptive input influenced by cognitive, neurophysiological and environmental factors (Legrain et al., 2002; Tracey and Mantyh, 2007). Consequently, both the perceptual and the brain responses evoked by pain exhibit considerable natural variability both between individuals and across multiple experimental trials (Coghill et al., 2003; Nielsen et al., 2009; Stancak et al., 2011). The perception of pain from nociception is generated by a spatially-distributed network of brain regions (Apkarian et al., 2005; Peyron et al., 2000) and recent fMRI studies have highlighted the importance of studying network dynamics for understanding the emergence of pain (Boly et al., 2007; Ploner et al., 2010). Such work reflects a conceptual shift towards an appreciation of the importance of understanding the functional architecture of the brain as represented by intrinsically connected networks (ICNs), whose regional activity is correlated during the resting-state, and modulated by external inputs (Smith et al., 2009). Pain stimulation is therefore an ideal candidate system in which to investigate the ability of multimodal neuroimaging to provide trial-by-trial spatiotemporal dissociation between regional

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brain responses to stimulation, and to probe the contribution of network dynamics to the brain response.

The importance of brain network dynamics in supporting cognitive function is becoming increasingly clear (Bressler and Menon, 2010). We broadly summarise the contribution of ICN dynamics to task performance and behavioural outcomes at three spatio-temporal scales as: 1) (*Ongoing*) facilitating short-term, network response priming such that pre-stimulus ICN activity influences the behavioural and/or brain response to a subsequent stimulus (Becker et al., 2011; Sadaghiani et al., 2009); 2) (*Concurrent*) providing an active contribution through signalling occurring during task performance (Fox et al., 2007; Kelly et al., 2008); 3) (*Intrinsic*) defining core properties of ICNs, such as resting-state signal coherence, that determine parameters of behavioural (Mennes et al., 2011) or brain responses (Kannurpatti et al., 2012; Keller et al., 2011).

Here we use simultaneous EEG–fMRI recordings during rest and fixed-temperature, noxious, thermal stimulation to investigate the contributions of these three mechanisms to the natural variability in behavioural and brain responses. EEG–fMRI presents a powerful tool to study this phenomenon as: 1) fMRI provides the high spatial resolution whole-brain coverage required to measure the activity of the distributed brain areas that comprise ICNs; 2) EEG records the dynamics of brain activity directly, providing measurements of neuronal response features with high temporal resolution. This allows investigation of how variability in these features correlates with regional haemodynamic response amplitudes; 3) Indices of cortical excitability, such as the 8–13 Hz alpha oscillation which has been shown to modulate subsequent behavioural and brain responses (Becker et al., 2011; Hanslmayr et al., 2007; Linkenkaer-Hansen et al., 2004), can be measured from EEG and their effect upon simultaneous fMRI signals observed.

It is important to characterise both inter- and intra-subject response variability in order to fully understand the link between the brain's response to pain and the subjects' perception of pain. However, the majority of neuroimaging studies analyse only a subset of potential functional indices which restricts interpretation of the complex and parallel brain processes underlying a given behaviour. In this study we aim to take a more comprehensive approach, by investigating the influence of multiple ICNs at a range of temporal scales. This demands both a multimodal neuroimaging approach and an integrative analysis framework, combining the dynamics of pre- and peri-stimulus neuroelectric and haemodynamic ICN activity with event-related responses. We utilise three analysis strategies: 1) investigating the Intrinsic mechanism through the relationship between task-evoked fMRI responses in the pain network and the resting-state functional connectivity of this network; 2) studying the Concurrent mechanism by investigating the origins of the natural variability in the brain's response to pain stimulation using GLM analyses featuring single-trial parametric modulations of either pain-ratings or EEG evoked potential amplitudes. Additionally, the modulation of the fMRI response to pain by Ongoing cortical excitability is tested by integrating spontaneous EEG alpha-power with stimulus timings in the GLM; 3) using model-free independent components analysis to identify ICNs additional to the pain network and investigating how their fMRI signal modulations vary with the pain fMRI response, the EEG response and the behavioural response. Studying pre- and post-stimulus fMRI signals in these ICNs provide a method to identify the influence of Ongoing and Concurrent mechanisms respectively. Using these methods we demonstrate for the first time that multiple, spatio-temporal brain processes contribute to the subjective experience of pain.

Materials and methods

Experimental paradigm

Simultaneous EEG–fMRI data were recorded in 16 subjects (8 female, mean age \pm SD 24.3 ± 3.8 years). Written informed consent

was obtained from all participants and the protocol was approved by the Research Ethics Board of the University of Birmingham. Thermal pain stimuli were applied to the perineal area of the right leg at two temperature conditions (PATHWAY CHEPs, Medoc, Israel). Rapidly delivered, noxious contact heat stimulation activates both A δ - and C-fibre mechano-heat skin nociceptors leading to robust and reproducible fMRI responses in the pain network (Roberts et al., 2008) and well characterised contact heat evoked potentials (CHEPs, (Chen et al., 2001; Warbrick et al., 2009)). During a preliminary testing session, immediately prior to scanning, the high condition was selected as the stimulus temperature that elicited an average subjective pain report of 7/10 on a numerical rating scale (NRS), high temperature was 53 °C (3 subjects); 52 °C (10 subjects); or 51 °C (3 subjects). The low temperature condition was always set 2 °C below the high, and elicited an average subjective pain report of 4/10. During a twelve-minute experimental run, thirty-six stimuli of one temperature condition were delivered separated by an inter-stimulus interval of 20s. Two experimental runs were acquired for each temperature, resulting in seventy-two trials per condition. Run order was counterbalanced across subjects. Individual trials consisted of a single thermal pain stimulus followed by 12 s of central fixation before a visual cue (6 s central display of the word “Rate”) instructing the subject to report a behavioural pain rating using a 0–4 NRS (0 = no pain and 4 = severe pain). Between stimuli the baseline temperature of the thermal probe was maintained at 32 °C. Stimuli were delivered to exactly the same area of the leg for two consecutive stimuli and then the probe was moved to an adjacent area to prevent sensitisation to the stimulus. Within the same session, following the first two stimulus runs, a six-minute resting-state scan was also acquired, during which subjects were instructed to lie still, keep their eyes open and think of nothing in particular.

Data acquisition

All experiments were conducted at the Birmingham University Imaging Centre (BUIC) using a 3 T Philips Achieva MRI scanner. An eight channel phased-array head coil was used to acquire T1-weighted anatomical image (1 mm isotropic voxels) and whole-brain T2*-weighted, functional EPI data ($3 \times 3 \times 4$ mm voxels, TR = 2000 ms, TE = 35 ms, SENSE factor = 2, flip angle = 80°). Cardiac and respiratory cycles were continuously recorded (pulse oximeter and respiratory belt). EEG data were recorded from 62 scalp Ag/AgCl ring-type electrodes distributed according to the 10–20 system with two additional channels used for recording the ECG and electrooculogram. The impedance at all recording electrodes was maintained below 20 k Ω . A BrainAmp MR-plus EEG amplifier (Brain Products, Munich) was used for recording data at 5 kHz with 0.016–250 Hz hardware filters. Subjects were positioned such that electrodes Fp1 and Fp2 were at the magnet isocentre in the foot/head direction so as to minimise gradient artefact (Mullinger et al., 2011). The EEG clock was synchronised with the MR scanner clock, with the TR equal to a multiple of the EEG sampling period, to ensure consistent sampling of the waveforms (Mullinger et al., 2008).

EEG analysis

EEG data were corrected for MRI gradient and pulse artefacts using average-artefact subtraction in Brain Vision Analyser 2 (BrainProducts, Munich). Data were subsequently down-sampled (500 Hz), filtered (1–30 Hz) and converted to average-reference. For each subject, data were concatenated across all four thermal stimulus runs and processed with independent component analysis (fastICA (Hyvarinen, 1999)). Components with non-physiological power spectra or scalp distribution that represented residual pulse or eye-blink artefacts were removed.

Measuring continuous and pre-stimulus alpha power

To ensure accurate measurement of the continuous alpha oscillation only ICs with bilateral parietal/occipital scalp topography and a clear spectral peak presenting 8–13 Hz alpha power were selected and retro-projected into channel space. Data from parietal/occipital channels PO3/4, POz, O1/2 and Oz were epoched based on the MRI trigger (0–2000 ms). The Fast-Fourier Transform was used to calculate the power spectral density for each TR epoch, averaged within ± 1 Hz of the individuals' alpha frequency (IAF). Separately for each run, the alpha power timecourse was averaged across the six channels and then normalised to control for differences in maximum power between subjects. This timecourse was then mean subtracted to create a regressor for general linear model (GLM) analysis. Furthermore, the pre-stimulus alpha power was calculated from the mean power within a 500 ms time window immediately preceding the delivery of each thermal stimulus. Additionally, data were epoched around the stimulus timings (−2 to +3 s) and time-frequency spectrograms of oscillatory power were calculated for all single-trials using the continuous Morlet wavelet transform in the Fieldtrip toolbox (<http://fieldtrip.fcdonders.nl/>) (Oostenveld et al., 2011). Spectrograms were averaged across all trials and subjects to visualise alpha power dynamics both pre and post-stimulation.

Single-trial CHEPs

Single-trial epochs (−500 ms pre-stimulus to 1000 ms post-stimulus) were extracted from channel Cz which displayed the maximum evoked response in each subject and baseline corrected based on the pre-stimulus period. Trials with amplitude exceeding ± 100 μ V at any timepoint were rejected. Single-trial CHEPs N2–P2 amplitudes were measured using an automated linear regression method (Mayhew et al., 2006). Separately for each experimental run, regressors for GLM analysis were formed from the mean-subtracted parametric modulations in N2–P2 amplitude. For rejected trials, amplitude values were set to the mean value of the run (i.e. zero).

Sorting trials by CHEPs amplitude, pain ratings and alpha power

To investigate the relationship between the CHEPs waveform, the pain experience and ongoing brain activity and also to facilitate later comparison with the timecourse of BOLD responses, single-trial CHEPs were separately sorted by single-trial N2–P2 amplitude, pain rating and pre-stimulus alpha power. Trials were binned into quartiles according to the lower 25%, median 25% (37.5–62.5%) and upper 25% of the respective variable.

fMRI GLM analysis

All fMRI analyses were carried out using FSL 4.1.8 (www.fmrib.ox.ac.uk/fsl). Prior to statistical analysis automated brain extraction and motion correction were applied. Physiological noise correction was performed using custom MATLAB code (Glover et al., 2000), followed by slice-timing correction, spatial smoothing (5 mm FWHM Gaussian kernel), high-pass temporal filtering and registration to high-resolution structural and MNI standard brain images. Three subjects were discarded from further analyses due to multiple sharp movements (>3 mm) that resulted in poor EEG and fMRI data quality.

Single-trial CHEPs–BOLD or rating–BOLD correlations

GLM analyses were performed to identify brain regions where the BOLD response amplitude correlated with single-trial variability in either: I) CHEPs N2–P2 amplitude; or II) the subjects' behavioural rating of pain intensity. A design matrix was constructed for each run using three regressors: 1) constant amplitude thermal stimulus; 2) stimulus parametric modulator of either N2–P2 amplitude or behavioural pain rating; 3) 6 s NRS periods to account for the motor action of stimulus rating.

Alpha power–BOLD response interaction

A separate GLM analysis was performed to identify brain regions where the amplitude of the BOLD response to thermal stimulation was modulated by the brain's spontaneous cortical excitability as indexed by ongoing EEG alpha power (Romei et al., 2008). We addressed this question by using the GLM to model an interaction between the stimulus timings and alpha power, analogous to the psychophysiological interaction (PPI) method (Friston et al., 1997). The multiplication of the constant amplitude stimulus regressor and the alpha power creates an additional regressor, the amplitude of which is non-linearly larger during a state of high alpha power and smaller during low alpha power. First-level activation maps were generated using four regressors: 1) main effect of continuous alpha power; 2) main effect of constant amplitude thermal stimulation; 3) the interaction between the stimulus and continuous alpha power, modelled as the element-wise multiplication of columns (1) and (2); 4) 6 s NRS rating periods.

All regressors were convolved with the canonical double-gamma haemodynamic response function and first-level statistical analyses were performed using FEAT 5.98. Positive and negative contrasts were set on all regressors. Separately for high and low temperature conditions, first-level results were combined across both runs, to calculate an average response per subject at the second-level with fixed effects, and then combined across all subjects at the third-level using FLAME 1 + 2 mixed effects (Woolrich et al., 2004). All Z-statistic images were thresholded using clusters determined by a $Z > 2.0$ and cluster corrected significance threshold of $p < 0.05$.

fMRI ICA analysis

In order to investigate the contributions of activity in multiple brain networks to variability in the response to pain we used independent component analysis (ICA) to resolve coherent patterns of fMRI signal fluctuation without the a-priori assumptions about the shape or timing of the response that are inherent in the GLM. BOLD data from all high temperature stimulation runs were temporally concatenated and a group MELODIC analysis was used to decompose the data into 20 maximally independent spatial maps and their associated time-courses (Beckmann and Smith, 2004). Five ICs were selected for further analysis, based on their spatial similarity to previously reported ICNs: 1) pain network (including thalamus, insula, anterior cingulate, bilateral prefrontal cortex and parietal operculum), this ICN corresponds to the recruitment of the resting-state saliency ICN (Menon and Uddin, 2010; Seeley et al., 2007) by a pain task (Legrain et al., 2011); 2) primary sensorimotor; 3) visual; 4) dorsal attention network (DAN) (Corbetta and Shulman, 2002); and 5) DMN. Dual-regression (Beckmann, 2009) was then used to identify individual subject timecourses for each ICN. Timecourses were epoched based on the stimulus timings (−2 to 20 s) to create single-trial ICN HRs. These HRs were converted into percent signal change using the mean value of the final two time points of the subject's mean ICN HR as baseline. For each subject and each ICN, these single-trial HRs were then separately sorted by the corresponding quartiles of N2–P2 amplitude and pain rating.

Statistics

Separately for the sorted CHEPs and ICN HR trial timecourses, two-way repeated measures (RM) analysis of variance (ANOVA, factors: sorted quartile \times time) were first used to investigate whether a significant effect of quartile or an interaction between time and quartile was present. Subsequently, at each EEG/HR time-point a one-way RM ANOVA was used to test for significant difference in response amplitude between quartiles. Significant differences between the quartiles of pain rating were tested with one-way ANOVA.

ROI definition and timecourse extraction

We investigated the relationship between the amplitude of the BOLD response evoked by thermal pain stimulation and the functional connectivity between the major nodes of the pain network in the resting state. Regions of interest (ROIs) were defined in MNI space from the group-level GLM statistical map of significant BOLD response to thermal stimulation. To ensure comparison of equal voxel volumes between subjects and regions, all ROIs were formed by centering a $3 \times 3 \times 3$ voxel cube ($9 \times 9 \times 12$ mm) on the maximum z-statistic voxel in the following areas: contralateral anterior insula (AntIns), contralateral secondary somatosensory cortex (SII), anterior cingulate cortex (ACC) and thalamus. The following ROIs were defined as non pain-processing, control areas from the group ICN statistical maps: left and right primary visual cortex, left and right posterior parietal nodes of the DAN, and the precuneus/posterior cingulate (PCC) and superior frontal gyrus (SFG) nodes of the DMN. All ROIs were separately registered to the resting-state and stimulation runs of each individual subject using FLIRT and the average timecourse across voxels was extracted for each run. Stimulus run timecourses were then epoched based on the stimulus timings (-2 to 20 seconds) to create single-trial BOLD HRs. These HRs were converted into percent signal change using the mean value of the last two time points of the subject's mean HR as a baseline. The evoked BOLD amplitude was calculated for each trial as the maximum signal change occurring in a 10s window post-stimulus.

Functional connectivity of resting-state BOLD data

Seed-based functional connectivity (FC) analysis was performed to investigate the strength of correlation in BOLD signal between ACC, SII and AntIns ROIs during the independent resting-state run. Following previous methodology (Fox et al., 2005), BOLD data from the separate resting-state scan were pre-processed using brain extraction, motion correction, physiological noise correction for respiratory and cardiac cycles based on the RETROICOR method (Glover et al., 2000) using in-house MATLAB code, low-pass filtering ($0.008 < f < 0.08$ Hz) and 5 mm spatial smoothing. The following trends of no-interest were removed with linear regression: six motion parameters, global signal calculated by averaging across all voxels, ventricular and white-matter signals. For each ROI in turn, the BOLD signal was averaged across all voxels to create a seed timecourse that was then correlated with the timecourse of all other brain voxels. To explicitly assess the magnitude of FC between a pair of ROIs, the mean Pearson's correlation coefficient (R) across voxels was calculated. The mean FC was then correlated with the peak amplitude of the mean BOLD response to the stimulus, extracted from the thermal stimulation BOLD data using the same ROIs. As a control analysis we tested whether the stimulus evoked BOLD response in pain ROIs was related to the resting FC between the following non pain-processing regions: left and right primary visual cortex; left and right posterior parietal nodes of the DAN; and the PCC and SFG midline nodes of the DMN.

Results

EEG and pain ratings

A robust CHEPs N2–P2 response was observed to high temperature stimuli in all subjects but only in seven subjects for the low temperature condition. Although all subjects reported a similar sensation, we hypothesize that the low temperature stimuli did not reliably stimulate the “first-pain” conducting A δ -fibres in all subjects. Group average CHEPs waveforms are displayed in Fig. 1A. Both group mean CHEPs N2–P2 amplitude and pain rating were significantly larger for high than low temperature stimuli (Fig. 1B, $p < 0.05$ and $p < 0.001$ respectively, paired two-tailed t -test). Only one instance of

a significant ($p < 0.05$) positive correlation between single-trial pain ratings and N2–P2 amplitudes was observed for high and low temperature data (different subject). Range of R values, low: -0.1 to 0.23 ; high: -0.12 to 0.24 . No significant correlation was observed between pre-stimulus alpha power and pain rating, range of R values, low: -0.05 to 0.1 ; high: -0.06 to 0.08 .

fMRI

GLM analysis showed significant positive BOLD responses (PBR) to constant amplitude thermal stimulation in: brainstem, thalamus, cerebellum, bilateral insula cortex, bilateral orbito-frontal cortex (OFC), ACC, mid cingulate cortex (MCC), bilateral SII, bilateral primary somatosensory cortex (SI), bilateral pre-central gyrus, bilateral supramarginal gyrus, and SMA (Fig. 2 and Table 1). These areas are consistent with previous reports of the distributed brain network activated by pain processing (Legrain et al., 2011; Peyron et al., 2000; Tracey and Mantyh, 2007) and are highly comparable to those previously reported for contact heat stimulation (Roberts et al., 2008). Significantly larger PBR to high temperature stimuli compared to low temperature were observed in small regions of contralateral insula and SII cortex only (data not shown). We focus subsequent analyses on the high temperature stimuli as these provided the most robust EEG responses and HR amplitudes between high and low temperature conditions were similar.

EEG–fMRI correlations

Single-trial amplitude variability of the CHEPs N2–P2 explained the BOLD response better than the constant amplitude regressor in areas of the cerebellum, bilateral insula, MCC, ACC, bilateral SII, bilateral SI, SMA and precuneus during the high temperature condition (Fig. 2A). The spatial extent and significance of CHEPs–BOLD correlations was larger in the posterior than the anterior insula. These results extend previous EEG source localisation studies that identified bilateral insula/SII and cingulate cortex as sources of the N2–P2 response to noxious stimulation (Bromm and Chen, 1995; Tarkka and Treede, 1993; Valeriani et al., 2002). The spatial extent of CHEPs–BOLD correlation in bilateral SI was much greater than was observed for the main effect of thermal stimulation. The precuneus and contralateral pre-central gyrus were the only brain regions where BOLD responses significantly correlated with variability in CHEPs amplitude but not with the constant amplitude, main effect of thermal stimulation.

Pain–fMRI correlations

GLM analysis also demonstrated single-trial parametric modulations in BOLD signal that positively correlated with variability in subjects' behavioural pain rating in SFG, MCC, ACC, contralateral precentral gyrus, bilateral SI and SMA (Fig. 2B). Brain areas that correlated with pain rating but not with CHEPs variability were the dorsal ACC and SFG.

BOLD signal in ICNs is modulated by CHEPs amplitude

Group ICA analysis, with no a-priori model of brain activity, revealed patterns of coherent fluctuations in fMRI signal due to ongoing brain processes and stimulus modulations. The DMN, DAN and visual ICNs were additional to the pain and sensorimotor ICNs detected by the GLM, a discrepancy that we attribute to a combination of the considerable trial-by-trial amplitude variability and non-canonical morphology of the haemodynamic response in these regions. Analysis of HR timecourses showed that all ICNs exhibited stimulus-locked changes in BOLD signal. The pain and sensorimotor networks and the DAN responded to thermal pain with increases in BOLD signal compared to pre-stimulus baseline, whereas negative BOLD responses

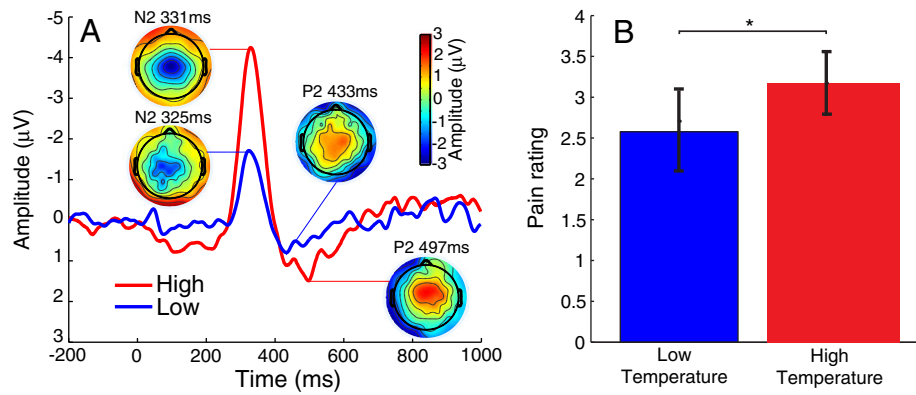


Fig. 1. Group mean CHEPs (A) and pain ratings (B) for low (blue) and high (red) temperature trials. Stimulation occurred at time = 0 ms. The scalp distribution of EEG amplitude at the N2 (low: 325 ms; high: 331 ms) and P2 (low: 433 ms; high: 497 ms) peak latencies showed a centralised spatial pattern typical of vertex maximal CHEPs for both low and high temperatures. N2–P2 amplitudes and pain ratings (*) were significantly larger for high temperature stimuli than low (both $p < 0.001$). Error bars represent \pm standard error in the mean.

were observed in the visual network and DMN. We investigated how modulation of HRs extracted from these ICN was related to evoked CHEPs and pain response. A substantial difference in the CHEPs waveform between quartiles of N2–P2 amplitude trials was clearly evident (Fig. 3A, upper left). Pain ratings of the corresponding trials revealed a non-significant ($p = 0.08$, RM ANOVA) trend for higher pain ratings concurrent with larger amplitude CHEPs.

Sorting the single-trial ICN HRs according to the N2–P2 amplitude of CHEPs showed that the activity of all of these networks was modulated in a graded way. A significant interaction (two-way ANOVA) between CHEPs-quartiles and time-point was observed for CHEPs and Pain, Somatomotor, DAN and DMN ICN timecourses. Significantly increased PBR in upper compared to lower N2–P2 amplitude quartile trials was observed in the pain, sensorimotor and DAN ICNs ($p < 0.05$,

RM ANOVA) (Fig. 3A). The DMN response to thermal pain was also modulated with CHEPs, with a significantly reduced magnitude of negative BOLD response (10–12 s) observed in trials with highest N2–P2 amplitude. Interestingly, a significant difference in DMN amplitude between quartiles was also observed in the pre-stimulus ($-2-0$ s) HR timepoints ($p < 0.05$, RM ANOVA), indicating that trials where the DMN BOLD signal was more positive at the time of stimulation had significantly smaller CHEPs N2–P2 amplitude. This suggests a connection between the activity in the DMN and the electrophysiological response to the subsequent pain stimulus. The link found here between DMN activity and CHEPs amplitude may therefore be suggestive of a mechanism by which perceived stimulus saliency is coded. This effect was investigated more directly using the pain ratings themselves.

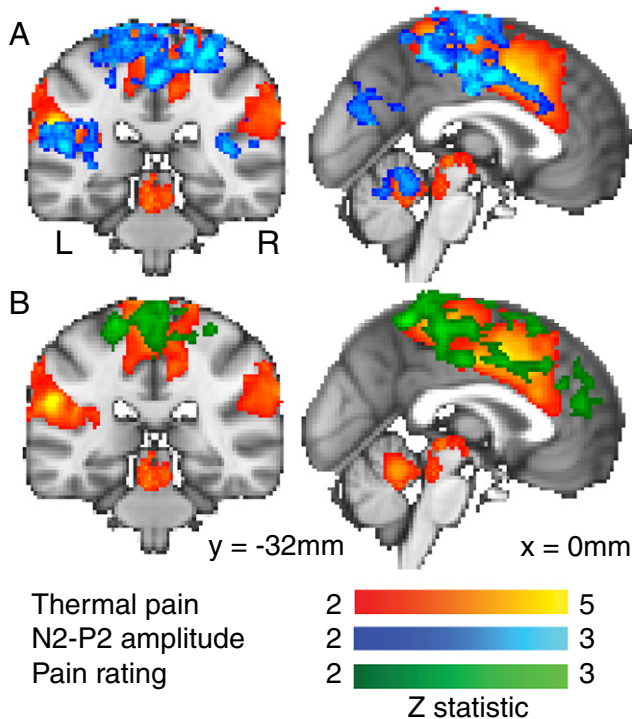


Fig. 2. Group mixed-effects BOLD response to the main effect of constant amplitude thermal pain stimulation (red-yellow) superimposed with: A) significant positive correlation between single-trial amplitude of the high temperature CHEPs N2–P2 and the BOLD response (blue); B) significant positive correlation between single-trial pain ratings and the amplitude of the BOLD response (green) combined across high and low stimulation temperatures. All statistical maps are cluster corrected $Z = 2.0$, $p < 0.05$.

Table 1

MNI co-ordinates of the peak z-statistic voxel for all significantly activated brain areas identified from GLM analyses (Figs. 2 & 4). Peak locations are reported for both hemispheres for bilateral activations, with just one peak location presented for midline activations. Shaded rows display peak voxels identified from the positive BOLD response to constant amplitude thermal pain (red), positive BOLD–CHEPs correlations (blue), positive BOLD–pain rating correlations (green) and the conjunction between DMN ICN and alpha–BOLD interaction (yellow). NA indicates that significant voxels were not observed in that hemisphere.

ROI	Left hemisphere				Right hemisphere			
	x	y	z	Z-stat	x	y	z	Z-stat
Thalamus	–6	16	0	2.75	4	–20	0	2.65
Anterior insula	–34	22	–6	4.24	40	24	–8	4.81
Posterior insula	–40	–16	–2	4.32	40	–8	–8	4.56
ACC	NA	NA	NA	NA	4	16	46	4.94
MCC	–6	–10	40	4.28	NA	NA	NA	NA
SII	–56	–28	20	5.34	62	–30	24	3.08
SI	–8	–26	68	4.02	18	–42	68	4.36
Pre-central gyrus	–28	–10	48	2.42	46	0	42	2.65
Supramarginal gyrus	–56	–30	26	4.47	50	–42	46	4.25
SMA	NA	NA	NA	NA	2	–20	64	3.85
OFC	–44	42	16	3.31	44	42	10	3.26
Anterior insula	–38	8	–6	2.43	32	12	–8	2.72
Posterior insula	–40	–4	–8	2.90	34	–18	2	2.68
ACC	NA	NA	NA	NA	2	14	38	2.76
MCC	–2	–6	40	3.12	NA	NA	NA	NA
SII	–50	–34	22	2.94	48	–38	16	2.32
SI	–16	30	68	3.31	20	–30	64	3.26
Pre-central gyrus	–38	–12	42	2.82	NA	NA	NA	NA
SMA	0	–22	64	3.46	NA	NA	NA	NA
Precuneus	–10	–56	30	2.94	NA	NA	NA	NA
ACC	NA	NA	NA	NA	2	18	40	3.23
MCC	NA	NA	NA	NA	2	16	42	3.41
SMA	–4	–30	64	3.17	NA	NA	NA	NA
SI	–26	–38	64	3.71	28	–28	64	3.09
Pre-central gyrus	–24	8	48	2.52	NA	NA	NA	NA
Paraculate	NA	NA	NA	NA	–4	46	12	3.12
SFG	NA	NA	NA	NA	8	50	30	4.16
IPL	–48	–70	32	NA	50	–62	32	NA
Precuneus	–2	–44	26	NA	NA	NA	NA	NA
SFG	NA	NA	NA	NA	6	50	10	NA

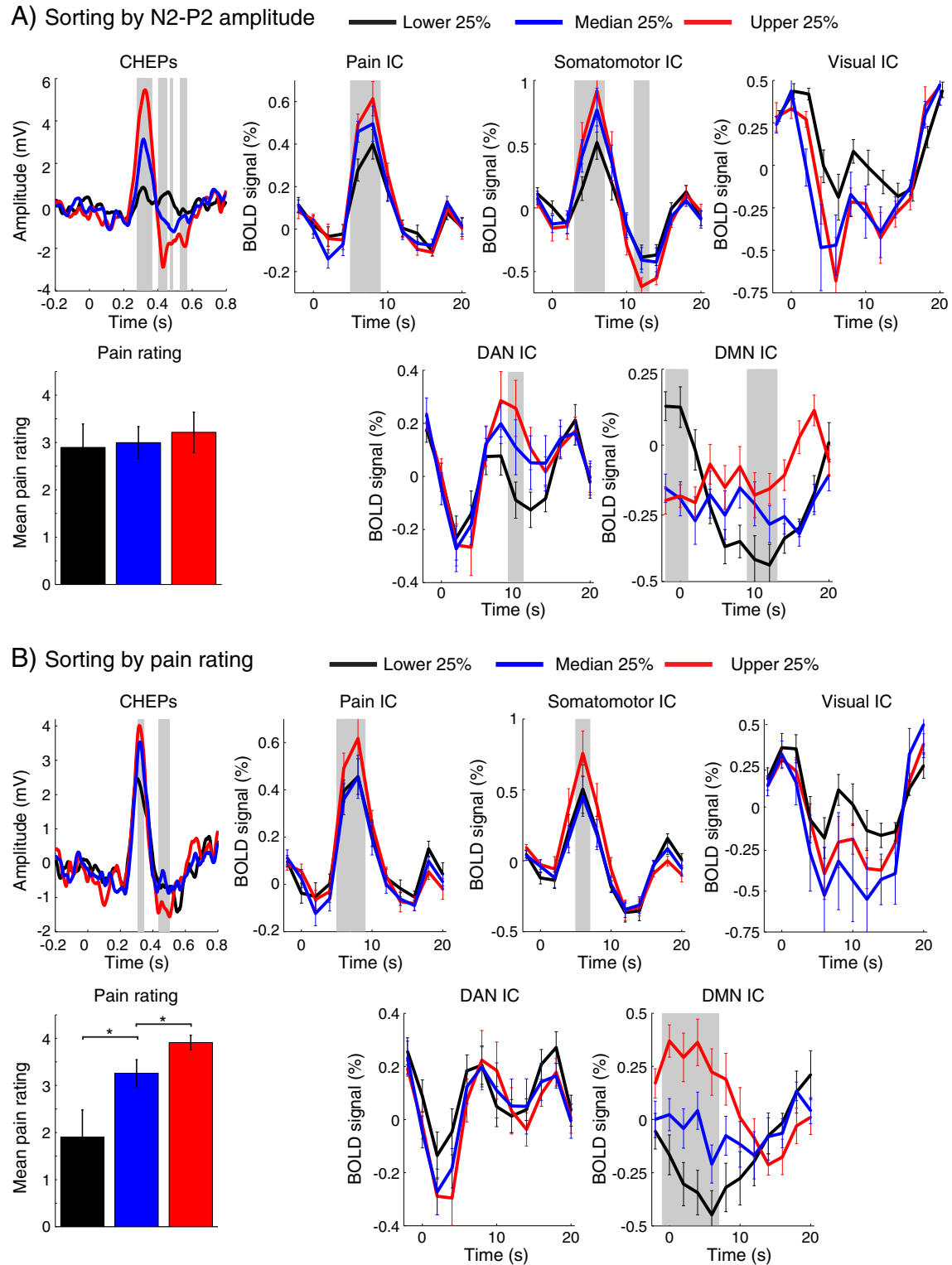


Fig. 3. Modulation of the haemodynamic response in the five ICNs by A) N2–P2 CHEPs amplitude and B) single-trial pain ratings. HRs are sorted by upper (red), median (blue) and lower (black) 25% quartiles of binned trials and averaged for display purposes. Error bars represent standard error in the mean across the group. Grey areas indicate the time points where a significant difference in amplitude between quartiles was observed, RM ANOVA $p < 0.05$. * indicates significant difference between quartiles of pain rating, RM ANOVA $p < 0.05$.

BOLD signal in ICNs is modulated by pain

The shape of the CHEPs waveform was similar between quartiles of pain-rating, however the sorting procedure reveals the temporal intervals that bear the strongest relationship to pain. These intervals

are centred on the N2 and P2 peaks, which show significantly larger amplitudes in trials with high pain ratings ($p < 0.05$) (Fig. 3B), in agreement with previous work (Chen et al., 2001). As expected, a very significant difference ($p < 0.01$, RM ANOVA) in pain rating between quartiles was observed. Sorting the single-trial ICN HRs by

the pain ratings also revealed significant effects in addition to those observed in the GLM analysis (Fig. 3B). A significant interaction between pain-quartiles and time-point was observed for CHEPs and Pain, Somatomotor and DMN ICN timecourses. In the pain network and DMN, a significant difference between the peak amplitude of the HRs sorted by upper, middle and lower quartiles of pain rating was observed ($p < 0.05$, RM ANOVA). Significant differences in DMN BOLD signal between quartiles were again observed for pre- and peri-stimulus time points (0–6 s). Trials that were perceived as more painful were associated with significantly larger BOLD signal amplitudes in the DMN at the time of stimulation. These analyses demonstrate that variance in the BOLD response in multiple ICNs can be explained by the variability in CHEPs and behavioural ratings and vice versa. In order to investigate other potential sources of variability, we further examined the effect of ongoing alpha oscillations and resting-state fMRI activity.

Modulation of CHEPs and DMN BOLD response by EEG alpha power

The group average, bilateral posterior scalp topography of alpha-power is shown in Fig. 4A. Fig. 4B displays the group average time-frequency spectrogram of the alpha oscillation, epoched around the stimulus delivery. The power of the alpha oscillation is consistent from two seconds pre-stimulus to three seconds post-stimulus, suggesting that our analysis has accurately extracted spontaneous alpha power. Fig. 4C shows the relationship between pre-stimulus alpha power and the amplitude of the CHEPs waveform. Upper quartile trials of pre-stimulus alpha power are associated with significantly

larger N2–P2 CHEPs compared to lower quartiles of alpha power. This finding is consistent with previous reports of the effect of alpha power upon evoked potentials (Becker et al., 2008; Reinacher et al., 2009). Fig. 4D demonstrates that a significant interaction between the amplitude of continuous alpha power and the BOLD response to thermal pain stimulation was observed in the DMN but not in any areas of the pain network. A significant interaction was also observed in visual cortex, a region where negative correlation between alpha power and BOLD signal has been previously reported (Goldman et al., 2002). These results indicate a specific relationship between the DMN response to pain and the intrinsic, ongoing state of the brain as indexed by the alpha oscillation. On average, thermal pain stimulation decreased the DMN BOLD response below pre-stimulus baseline levels (Fig. 3). Therefore, this result indicates that the magnitude of the DMN BOLD response to thermal pain was reduced, i.e. the DMN was less deactivated, during a state of high alpha power. This finding is consistent with three other results: the enhancement of CHEPs amplitude in trials with high pre-stimulus alpha power; the positive correlation between the amplitude of the CHEPs and the BOLD response in the PCC region of the DMN (Fig. 2A); and the association between larger CHEPs amplitude and less deactivation of the DMN (Fig. 3A).

Resting functional connectivity between pain network areas predicts stimulus-evoked response

Qualitatively similar group FC maps were observed when using either the ACC, SII or AntIns ROIs as the seed region, showing strong resting FC between all three ROIs similar to previous reports (Cauda

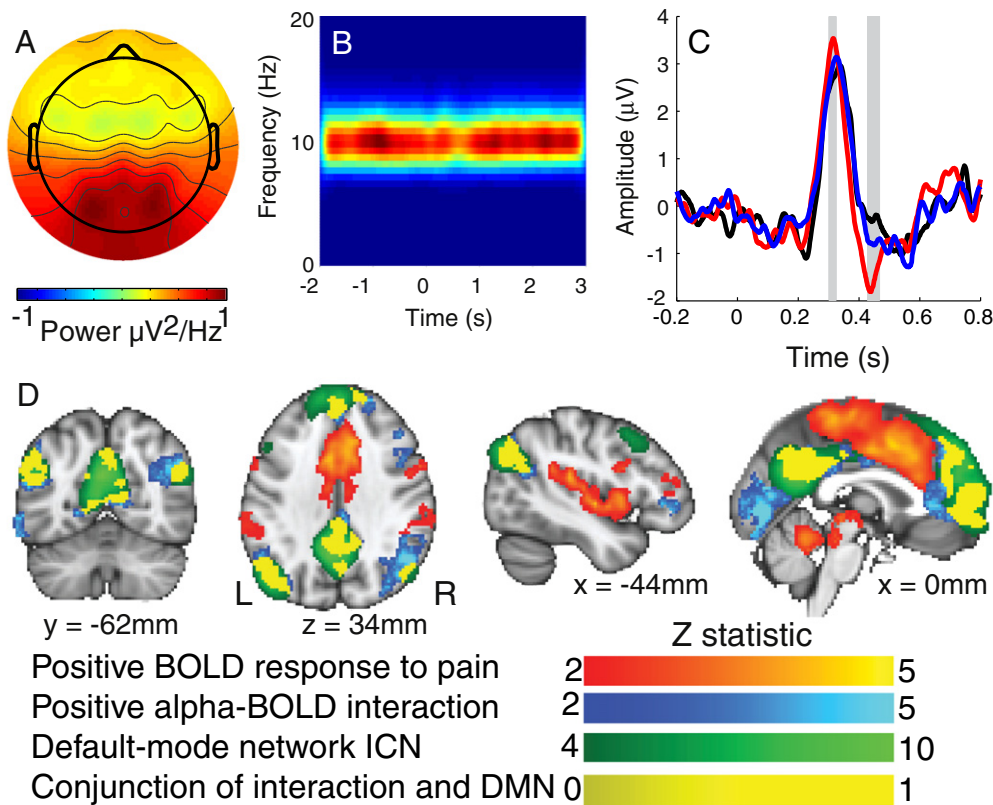


Fig. 4. Ongoing EEG alpha-power modulates CHEPs amplitude and interacts with the amplitude of the BOLD response to thermal pain in the DMN. Group average scalp topography of alpha power (A) and time-frequency spectrogram of alpha power relative to stimulation occurring at time = 0s (B). Modulation of CHEPs waveform by pre-stimulus alpha power (C). CHEPs trials were sorted by upper (red), median (blue) and lower (black) 25% quartiles of binned trials and averaged for display purposes. Grey areas indicate the time points where a significant difference in amplitude between quartiles was observed, RM ANOVA $p < 0.05$. D) Statistical maps present the group mixed-effects BOLD response to the main effect of thermal pain stimulation (red-yellow) overlaid with the positive interaction between alpha-power and the stimulus (blue); the group ICN of the DMN (green) and the conjunction between the interaction and the DMN ICN (yellow). Considerable spatial overlap between the alpha-interaction and the DMN independently identified by ICA was observed.

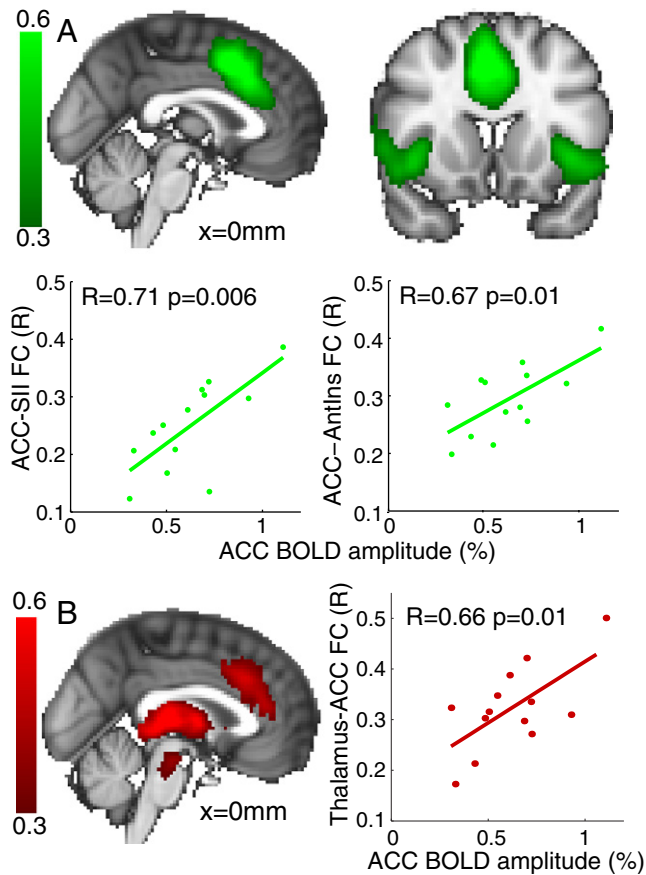


Fig. 5. Strength of resting-state functional connectivity within the pain network is correlated with the thermal pain evoked BOLD response. Group mean resting connectivity seeded in ACC (A green) and thalamus (B red). Significant correlation was observed between mean BOLD amplitude evoked by high temperature thermal pain condition in the ACC and the strength of pain network functional connectivity (A) ACC–AntIns and ACC–SII; B) ACC–thalamus during the separate resting-state scan.

et al., 2011; Kong et al., 2010). The strength of FC between both the ACC–AntIns and ACC–SII at rest was significantly positively correlated with the magnitude of the BOLD response to thermal stimulation in ACC (Fig. 5A). When seeding FC in the thalamus significant connectivity was observed only with the ACC (Fig. 5B). The strength of thalamus–ACC FC was also significantly correlated with the amplitude of the BOLD response to thermal stimulation in the ACC. No significant correlations were observed between the mean evoked BOLD amplitude in pain ROIs and the resting FC in any of the control regions (highest correlations: SII–V1, $R = -0.33$, $p = 0.26$; ACC–DMN, $R = 0.04$, $p = 0.88$; AntIns–DAN, $R = -0.16$, $p = 0.59$) demonstrating that the observed relationship between resting connectivity and BOLD response to thermal pain was specific to pain processing areas and is not a general property of the brain.

Discussion

Delivering a fixed-temperature, noxious stimulus input enabled us to demonstrate that Ongoing, Concurrent and Intrinsic ICN mechanisms all contribute to the natural inter- and intra-individual response variability that forms a fundamental but often overlooked feature of all psychological and neuroimaging studies. We investigated the relationship between subjective ratings of pain intensity, BOLD haemodynamic responses, EEG evoked potentials, EEG alpha-power, pre- and peri-stimulus BOLD signals in multiple ICNs, and resting-state functional connectivity. Dependent on brain region and time relative to stimulation, all of these factors contributed to the observed response

variability. Evidence for the contribution of the three mechanisms can be summarised as follows: *Ongoing*: 1) Pre- and peri-stimulus fMRI signals in the DMN are related to the magnitude of the subsequent pain network BOLD response, CHEPs amplitude and subjective pain ratings. 2) The amplitude of CHEPs and the DMN BOLD response to pain stimulation are modulated by the spontaneous power of the EEG alpha oscillation. *Concurrent*: 1) Single-trial pain ratings and evoked-potential amplitudes correlate with the BOLD response in sub-regions of the pain network. 2) BOLD responses to thermal pain stimulation in multiple ICNs are related to the trial-by-trial magnitude of pain ratings and CHEPs. *Intrinsic*: The amplitude of the BOLD response to thermal pain stimulation in pain network regions is correlated with the strength of functional connectivity between those same regions during the resting-state.

It must be remembered that considering any of these effects in isolation represents an oversimplification of the functional integration of the brain processes underlying the stimulus response. Our results demonstrate that several of these effects are overlapping, either spatially whereby two different effects are found to contribute to response variance in the same brain region (e.g. alpha power and pain rating in the DMN); or occurring in the same temporal period (e.g. BOLD signal modulation in multiple ICNs). Furthermore we reveal the importance of dynamic functional interactions between brain regions in shaping the subjective experience of pain and demonstrate that contributions of brain processes at multiple spatio-temporal scales should be considered to fully understand cognitive function.

Contributions to response variability in the pain network

Traditionally, BOLD responses to noxious stimulation have been used to define the pain network (Peyron et al., 2000). By using a combination of standard GLM, data-driven ICA and EEG–fMRI integration analyses, we demonstrate that BOLD response variability in different regions of this pain network is explained by behavioural and electrophysiological variability. Specifically, the single-trial fMRI response amplitude in MCC, ACC, S1 and SMA was positively correlated with both pain ratings and evoked potential amplitude variability, providing support for coupling between these measures (Mobascher et al., 2009). There has recently been debate about the extent to which the evoked potential and fMRI responses of these regions are specific to pain perception, compared to stimulus saliency (Legrain et al., 2011; Mouraux and Iannetti, 2009). Although our methodology does not allow us to discriminate between saliency and pain, the similar regional correlations with the BOLD response suggest pain ratings and evoked potential amplitude contain some common information. Despite this general agreement, there were some dissociations with ACC and SFG being specifically correlated with pain ratings and insula with N2–P2 variability. Additionally, although pain ratings and N2–P2 amplitudes were significantly different in high and low temperature conditions, BOLD responses only differed in contralateral insula and SII cortex. It is clear that all of the factors which relate fMRI to EEG have not been uncovered, and EEG–fMRI integration studies should always bear this in mind.

Our approach of moving the thermal probe every two-stimuli minimised potential confounds of stimulus sensitisation and habituation upon the measured responses. However, these changes in stimulus location will cause a variation in the number of activated nociceptors and also introduce an uncertain touch component due to slight differences in pressure between trials. These peripheral mechanisms represent an additional source of variability in the stimulus responses but not a systematic effect that can confound our results.

Widespread modulation of ICNs by pain stimulation

Model-free analysis revealed that extrinsic stimulation extensively perturbs multiple networks that are widely distributed throughout

the brain. The DMN (Raichle et al., 2001) is the most widely studied ICN, preferentially engaged during rest and displaying task-induced reductions in activity during fMRI experiments (Hutchinson et al., 1999) that are commonly observed concurrently with task-related increases in signal in the DAN (Fox et al., 2005). Abnormal DMN BOLD coherence in chronic pain patients compared to healthy controls (Baliki et al., 2008) demonstrates a relationship between DMN activity and pain perception. Here we present the first temporal characterisation of DMN and DAN activity during painful stimulation. On average we observe BOLD signal increases in the DAN and reductions in the DMN. However, our results clearly indicate that the conventional concept of a standardised, consistent response does not fully represent the functional significance of activity in these ICNs. Trial-by-trial variability contains substantial information about pain processing which advances our understanding of the functional significance of the DMN in several ways.

Providing evidence of both Ongoing and Concurrent ICN influences upon brain and behavioural responses, higher pre- and peri-stimulus BOLD signal in the DMN was associated with the most painful stimulus trials and both increased latency and reduced amplitude of DMN deactivation (Fig. 3B). Previously, enhanced pre-stimulus DMN BOLD signal has been shown to facilitate successful stimulus perception (Sadaghiani et al., 2009). The observation of stronger DMN deactivations to stimulus trials perceived as less painful agrees with previous work (Kong et al., 2010) and suggests that the DMN response to the unique, subjective experience of noxious events that contain psychological components such as discomfort, threat and fear, is different to that evoked by cognitive tasks where the magnitude of DMN deactivation reflects the level of task engagement (Pallesen et al., 2009). A positive correlation was observed between the amplitude of single-trial CHEPs N2–P2 and the DMN and DAN BOLD response to thermal pain (Fig. 3A). We suggest that these results provide evidence that the mechanisms of attention and stimulus saliency that are known to induce natural variability in pain evoked potentials (Iannetti et al., 2008; Legrain et al., 2002), are represented in the fluctuations of DAN and DMN ICN activity. A further observation from our data is that trials where the pre-stimulus DMN BOLD signal was more positive were associated with smaller EEG response amplitudes but stronger pain ratings. We suggest that this apparent dichotomy represents an instance of dissociation between the evoked potential amplitude and the experienced pain (Iannetti et al., 2008; Mouraux and Iannetti, 2009; Ronga et al., 2013).

The amplitude of DMN BOLD signal at time of stimulation was found to be predictive of the subsequent pain rating and the amplitude of CHEPs and the BOLD response in both pain network and DMN regions. The magnitude of DMN deactivation has been previously linked with the level of demand or engagement in task performance (McKiernan et al., 2006; Pallesen et al., 2009; Singh and Fawcett, 2008) and reduced DMN activation is associated with response errors and poor task performance (Eichele et al., 2008; Weissman et al., 2006). The functional interactions between the DMN and regions of the attention network occurring concurrently with the task have been shown to predict task performance (Fornito et al., 2012; Prado and Weissman, 2011). In accordance with this previous work, our data suggest that DMN activity can play a central role in supporting brain function, can modulate behaviour and exert influence upon the processing of spatially distinct brain regions, including the pain network. We suggest that a rich, complex relationship exists between the activity of the DMN and the behavioural and brain response to acute pain stimulation and that the DMN can shape the perceptual significance of the stimuli.

Interaction between EEG alpha power and DMN BOLD response to pain

EEG–fMRI signals provide a wealth of complementary information and simultaneous recordings have the potential to reveal greater information about brain function than is available to either technique alone (Debener et al., 2006; Mayhew et al., 2012). However, the

different neurophysiological origin of the two signals necessitates careful experimental design and interpretation. For instance, synchronous neuronal activity with a low metabolic cost could potentially be invisible to fMRI but measured by EEG, or asynchronous yet energetically demanding neural signalling could be obscured in EEG but well represented in fMRI. Additionally, significant BOLD signal correlations with an EEG response do not necessarily represent the brain regions generating the EEG response but may simply reflect regions whose activity covaries with EEG signal variability. Provided these considerations are observed, EEG–fMRI represents a powerful tool for studying spontaneous brain dynamics with high spatiotemporal detail. This is illustrated by our second demonstration of Ongoing ICN influences, in that the DMN fMRI response to thermal pain stimulation depends on its interaction with the ongoing alpha oscillation. The magnitude of the BOLD deactivation in the DMN was significantly reduced during a state of enhanced alpha-power amplitude. This indicates that alpha power, an index of subjects' arousal and cortical excitability (Romei et al., 2008), also provides an index of the responsiveness of the DMN network to pain, and that alpha oscillations could represent a correlate of DMN-related processes in certain circumstances. DMN fluctuations are posited to reflect either externally-directed monitoring of the environment, or internally-directed mentation (Buckner et al., 2008), both of which could be associated with fluctuations in subjects' susceptibility/responsiveness that would affect the saliency of an external stimulus. As such the ongoing synchronisation/desynchronisation of alpha oscillations could be analogous to the fluctuations of activation/deactivation that are used to describe DMN function. In support of this hypothesis, a recent study (Mo et al., 2012) suggests that spontaneous fluctuations in resting-state alpha power reflect the antagonistic relationship observed between the task-negative (DMN) and task-positive (fronto-parietal, DAN) networks with fMRI (Fox et al., 2005).

Resting-state connectivity predicts amplitude of task-evoked BOLD response

Finally, we demonstrated effects of Intrinsic ICN mechanisms on brain responses by relating the functional properties of the resting pain network to its response to thermal stimulation. We defined pain ROIs from areas exhibiting a very significant PBR and show that inter-individual variability in the mean BOLD response peak-amplitude to noxious stimulation is explained by the functional connectivity between these ROIs at rest. Analogous to recent findings in motor cortex (Kannurpatti et al., 2012), subjects who had stronger resting-state FC between pain-responsive regions had a larger amplitude BOLD response to thermal pain stimulation in these same regions. This observation was true when assessing pain network FC between cortical insula, ACC and SII regions, as well as between the ACC and the thalamus, and was uniquely specific to the pain network. Resting FC of visual, DMN and DAN areas was unrelated to the BOLD response amplitude. No correlation was found between FC and the subjects' mean pain rating or N2–P2 amplitude in any of the investigated ROIs. This result demonstrates that part of the inter-individual variability in BOLD responses is explained by the intrinsic properties of the pain network. Taking this observation further, we would predict that the strength of pain network FC at the time of stimulation would account for additional intra-individual evoked and behavioural response variability, something that has been hinted at by recent studies (Boly et al., 2007; Cifre et al., 2012). Examining the resting-state or dynamic stimulus-related functional connectivity of the brain opens up new opportunities for studying how the ongoing activity of the brain modulates the stimulus response, and a technique which may be amenable to exploitation in clinical populations with a simple resting-state functional scan.

By exploiting natural inter- and intra-individual variability in behavioural and brain responses to constant intensity thermal pain stimulation we have demonstrated that electrophysiological and haemodynamic ICNs contribute to pain perception via all of the Ongoing, Concurrent and Intrinsic mechanisms suggested above. Our results add to the growing

body of evidence linking variability of neural responses and behavioural performance to low-frequency dynamics of ongoing brain activity measured by either fMRI or EEG. They also demonstrate the advantage of simultaneous EEG recording for interpreting and fully exploiting fMRI responses. Our approach of factoring contributions from multiple, interconnected brain processes is relevant to all studies which attempt to link evoked brain responses with behaviour, and demonstrates that exploiting these interactions leads to a more complete understanding of the brain's response to stimulation, and the psychophysiological emergence of the experience of pain.

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